Frequency of Histological Patterns of Renal Allograft Biopsies– One Year of Renal Allograft Experience

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ABSTRACT

Objective: To ascertain the frequency and spectrum of histopathological findings in renal allograft rejection cases received in one year.

Study Design: Cross-sectional study.

Place and Duration of Study: Histopathology Department of Armed Forces Institute of Pathology, Rawalpindi Pakistan from Jun 2020 to May 2021.

Methodology: Renal allograft rejection biopsy cases of 62 male and female patients between the ages of 15-60 years having undergone renal transplant with prior end-stage renal disease over one year were collected. Frequency and histopathological findings were studied after classifying them according to the Banff Classification.

Results: Cellular (T-cell mediated) rejection accounted for more than half of the cases under study, making it the most common cause of transplant rejection in our demographical area. It accounted for 28 (45.2%) slides of all the biopsies studied. Antibody-mediated rejection followed next with 17 (27.4%) slides, with seven slides (11.3%) of the cases borderline for changes accounting for a T-Cell mediated rejection. About 10 (16.2%) were non-specific changes negative for transplant rejection criteria.

Conclusion: Our study was instrumental in establishing rejection patterns and major rejection sub-types while classified under the Banff Classification in our demographical area. The cataloguing of the cases and the major underlying cause would help minimize rejection rates resulting in better clinical outcomes and increased patient survival.

Key Words: Renal transplant, Allograft rejection, Banff Classification.

INTRODUCTION

The end-stage renal disease remains one of the most debilitating medical conditions for patients of all ages.[1,2] Not only does it increase the burden of resources required due to the prolonged nature of the disease,[3] but it also results in significant patient morbidity and mortality even after regular dialysis and medical treatment.[1,4] The successful renal transplantation by Joseph Murray and his team in 1954 was a pioneering achievement in tackling this incapacitating disease and its complications.[5]

Renal transplant rejection continues to present a major obstacle to long-term allograft survival.[6] Alexis Carrell first coined the concept of rejection in the 1900s, and the term used was "biologic incompatibility".[7] The definition of rejection coins the idea of the donor's antigens being recognized by the recipient's immune system, warranting an immune response.[8] The diversity of this immune response results in various types and degrees of rejection, which is used as a diagnostic standard during renal biopsy specimens.[9]

Even though the pathological findings of renal graft rejection have been reported as early as the 1960s, no standard classification system was proposed until the early 2000s when in 1991, the Banff Classification was proposed to outline the standards for definition and grading of the type of renal allograft rejection.[9] Through subsequent meetings and modifications, the last one being in 2019, the Banff Classification is now considered the diagnostic standard to catalogue and classify this cases.[10]

The most recent Banff Classification has six categories outlined in Table-I. Among the six categories, the rejection categories are 2,3 and 4.[10] This study aims to classify diagnosed cases of renal allograft rejection received at our institute in the designated timeframe according to the Banff Classification since the frequency and type prevalent has never been studied in line with international standards and guidelines. This will provide a working skeleton and framework for future cataloguing of the various rejection types and working with clinicians and transplant surgeons to improve overall patient morbidity and mortality.

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Table-I: Banff Diagnostic Categories (Modified From Reference)[12]

Categories	
Category 1	Normal biopsy or non-specific changes
Category 2	Antibody-mediated changes
Category 3	Suspicious (borderline) for acute t-cell mediated rejection
Category 4	T-cell mediated rejection
Category 5	Interstitial fibrosis and tubular atrophy
Category 6	Other non-rejected changes

METHODOLOGY

This was a cross-sectional study carried out at the Histopathology Department of the Armed Forces Institute of Pathology, Rawalpindi Pakistan from May 2020 to June 2021. The sample size for the study was collected by a WHO calculator with a CI of 95% with a margin of error of 6%, keeping the population prevalence for allograft rejection at 4.1%, which was one-third of the international population proportion for renal graft rejection in our demographic area.[11]

Inclusion Criteria: All the male and female patients aged 30-60 years with a known primary renal disease resulting in ESRD requiring transplant and all cases of live related renal transplant (LRRT) were included in the study.

Exclusion Criteria: Inadequate biopsy (No glomeruli or a minimum of one artery cannot be identified) or an unfixed biopsy specimen were excluded from the study.

Renal allograft rejection biopsy cases of 62 male and female patients between the ages of 15-60 years having undergone renal transplant with prior end-stage renal disease over one year were collected. Frequency and histopathological findings were studied after classifying them according to the Banff Classification.[12] All the patients with sample selection were confirmed to have a known primary renal disease resulting in ESRD requiring a renal transplant.

Statistical Package for Social Sciences (SPSS) version 26.0 was used for the data analysis. Data was described in terms of range, mean ± SD, median, frequencies, and percentages.

RESULTS

A total of 62 biopsies were studied over one year. The mean age of the studied participnats was 36.79±10.65 years, with a range of 15-60 years. Of all the biopsies studied, the gender distribution comprised 49 (79%) males and 13 (21%) females.

The duration in which the rejection occurred post-transplant revealed that 34 (54.8%) samples were rejected within five years of the procedure, 2 (3.2%) samples were rejected between the sixth to the tenth year, whereas 26 (41.9%) samples were rejected post the tenth year of transplant. Frequency of transplant rejection types (classified according to BANFF classification) were shown in the Table-II.

Table-II: Frequency of Transplant Rejection Types (Classified According to Banff Classification) (n=62)

Banff classification types	Case Percentage n (%)
Normal biopsy or non-specific changes	10 (16.1)
Antibody-mediated changes	17 (27.4)
Suspicious (borderline) for acute t-cell mediated rejection	07 (11.3)
T-cell mediated cellular rejection	28 (45.2)

The data revealed that of all renal biopsies being studied under guidelines according to the Banff Classification, cellular rejection accounted for more than half of the cases under study, making it the most common cause for transplant rejection in our demographical area. It accounted for 28 (45.8%) samples of all the biopsies studied. Antibody-mediated rejection followed next with 17 (27.4%) cases, with 7 (11.3%) cases borderline for changes accounting for a T-Cell mediated rejection. Finally, about 10 (16.2%) samples accounted for non-specific changes negative for transplant rejection criteria.

Additional data collected revealed that a very small number of subjects under study, 2 (3.2%) samples had a history of a viral infection leading to the renal shutdown. The data also revealed that CNI (calcineurin inhibitor) toxicity was observed in 10 (16.1%) subjects post-transplant, leading to acute kidney injury. Acute T-cell mediated rejection (Tubulitis and interstitial inflammation) was shown in the Figure-1. Acute anti-body mediated rejection (Positive C4d staining) was shown in the Figure-2.
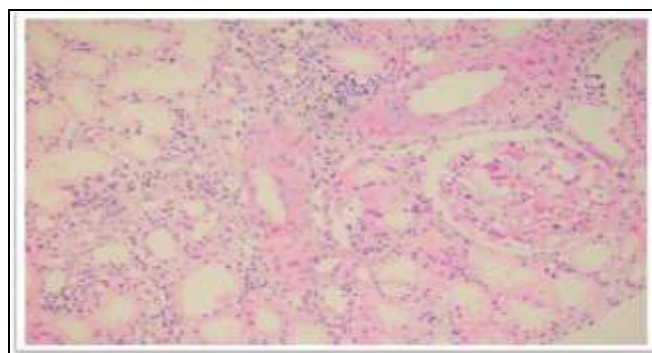

Figure-1: Acute T-Cell mediated rejection: tubulitis and Interstitial Inflammation
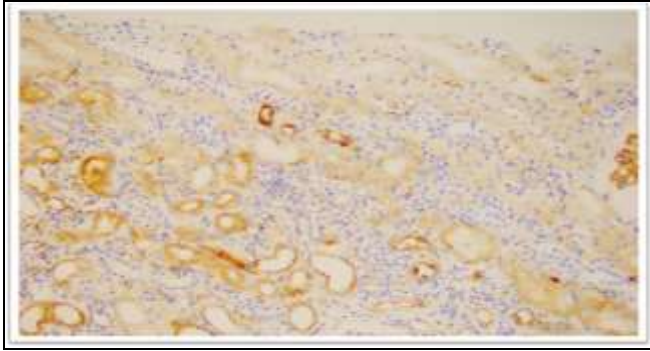
Figure-2: Acute Anti-Body Mediated Rejection: Positive C4d Staining

DISCUSSION

Renal transplant rejection remains a less documented subject in our demographic, with cases which remain underdiagnosed with respect to their histopathological characteristics owing to paucity of resources and diagnostic modalities only available even at very few centres of excellence.

Our study revealed a pre-dominantly male predilection which is in line with the available literature internationally.[13] Although gender specificity is seen in most renal transplant cases, the exact underlying genetic cause leading up to it is still unknown. Along with gender, the mean age of patients with rejection issues are usually between 20-40 years,[14] which was in line with the results obtained in our study (mean age: 36.79 ± 10.65 years).

With cellular rejection forming the major percentage of transplant rejection when studied with respect to the histopathological characteristics, our results show a similar pattern as seen internationally.[15] Furthermore, in line with data furnished internationally, antibody-mediated rejection followed cellular rejection as the leading cause in our demographical area as well.[16,17] Additional data gathered during our study revealed that the incidence of acute rejection (<3-6 months) was drastically less compared with previous studies. Even though the chances of rejection in the first five years were around 54.8%, the rejections during the first six months were less than 5% in our data. This has been attributed to superior facilities of better HLA matching and using live donors vs deceased, resulting in less cold ischemia time.[18,19] In addition, including ancillary molecular studies for diagnosing ABMR and identifying at-risk chronic patients has proved helpful worldwide. However, this facility is still under development in our setup. This includes microarray assessment of endothelial cells or NK gene expression.

Another matter of particular interest is the effect of calcineurin inhibitors as cornerstones for immuno-suppression in the early phase following renal transplantation.[20] Their adverse effect profile renders the transplant non-viable in certain cases by causing acute kidney injury and ultimately graft rejection. This toxicity is seen acutely, and its role in chronic rejection is controversial.[21] Acute CNI toxicity was seen in 16% of cases in our data analysis with resulting acute kidney injury and early graft rejection, the histo-pathological findings observed with the pre-dominant rejection type as discussed earlier.

Although significant progress has been made in our understanding of rejection pathogenesis and the refinement of morphological and histological criteria of Banff classification, several uncertainties remain. In the Banff classification, glomerulitis is characterized by endothelial cell enlargement and inflammatory cell infiltration resulting in narrowing and occlusion of lumina. However, inflammatory cells can be seen in non-ABMR conditions such as acute TCMR and glomerulonephritis. The quantification of inflammatory cells and minimal criteria of occlusion is not defined. In addition, Interstitial inflammation is defined by its extent. Therefore, it is impossible to determine if inflammatory cells are active or quiescent.

It is pertinent to mention here that in the most recent gathering for the BANFF review, it was proposed that the ear of artificial intelligence and machine learning would prove to be instrumental in better assessment, patient clustering and overall conformity to the set standards. However, this modality is only hampered by the subjective non-expertise and steep learning curve for the pathologists and clinicians currently employing the Banff classification. Making the modality more accessible and training professionals would further improve our subject conformity resulting in less variation and better results.[22]

CONCLUSION

Our study was instrumental in establishing rejection patterns and major rejection sub-types while classified under the BANFF Classification in our demographical area. The cataloguing of the cases and the major underlying cause would help minimize rejection rates resulting in better clinical outcomes and increased patient survival.

Conflict of Interest: None.

Author's Contribution

FA: Primary Author, Collected Data, MA: Critically reviewed artcile, IC: Intellectual analysis, peer reviewed, AAK: Initial concept, collected data, MA: Helped in statistical analysis.

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